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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/021,416	11/05/2001	Russell Phillips	R-236	1745

26619 7590 01/13/2005

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Applicati n N .	Applicant(s)	
	10/021,416	PHILLIPS ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Peri d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *1-4,11-15,22 and 24-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-10,16-21 and 23* is/are rejected.

7)☒ Claim(s) *10,19 and 20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11/05/2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Pri rity under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *07/02 03/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group II, claims 5-10,16-21 and 23 in the reply filed on 10/27/2004 is acknowledged. The traversal is on the ground(s) that it would not pose an undue burden to search certain of the groups together and certain other groups are closely related. This is not found persuasive because the different groups are related to products or methods that are patentably distinct from the transgenic animal, the cells, the method of making the animal and the method of using the animal that are all included in Group II. The products of the different Groups have different uses and the methods are all distinct from one another. For example, the method included in Group II is directed to in vivo screening for expression modulators of a secreted protein gene whereas Group III is directed to different methods requiring different assays to determine functional modulators and Group IV is directed to in vitro methods that are entirely different in methodology and technical considerations from the methods of Group II.

Specifically, Applicant has argued that the nucleic acid of Invention I is closely related to the cells, animal and methods of making and using the animal of Invention II. In particular, Invention I is directed to a gene targeting construct that is not necessary to disrupt a secreted protein gene in cells or in animals. Materially different constructs can be used to disrupt a secreted protein gene. The nucleic acid has patentably distinct uses including use as a probe or to express a polypeptide. Furthermore, the nucleic acid sequences of Invention I and the cells or the animals of Invention II are structurally and functionally different and have different uses. As such, Invention I and Invention II require materially different reagents and technical

considerations such that a proper search for both inventions would require an extensive search for materially different methods thereby placing an undue search burden upon the Examiner.

Applicant argues that a search of Invention I and any of Inventions III-XII would not be undue. In response, the nucleic acid construct of Invention I is not required for: the implementation of *in vivo* methods of identifying an agent that modulates the function of a secreted protein gene of Invention III, the *in vitro* methods of identifying an agent that modulates the expression of a secreted protein gene of Invention IV, the unknown agent of Invention V, the methods of identifying agents that modulate a secreted protein expression using a transgenic mouse comprising a disruption in a secreted protein gene of Invention VI, the methods of identifying an agent that modulates a secreted protein gene function using a cell comprising a secreted protein gene of Invention VII, the in vitro method of identifying an agent that has an effect on depression using a secreted protein of Invention VIII, the in vitro method of identifying an agent that has an effect on depression using a cell expressing or overexpressing a secreted protein gene of Inventions XI or X, the unknown agent of Invention XI and a method of treating depression in a patient of Invention XII, and vice versa. The nucleic acid of Invention I and products and methods of Inventions III-XII are classified differently. The burden required to search inventions I and any of Inventions III-XII together would be undue.

Applicant has argued that the Examiner has not provided a reasonable example of how the cells and animals of Invention II could be used in materially different processes so as to make the cells and animals of Invention II patentably distinct from Inventions III, IV and VI. In response, the methods of Inventions III, IV and VI are methods that differ from the method

of using the animals that is included in Invention II. It would require undue burden to search more than one distinct method with Invention II. Applicant argues that the cells of Invention III cannot be used as suggested by the examiner. However, Invention III is not directed to cells. The cells of Invention II, can be used to produce a secreted protein because the cell possesses genes encoding many secreted proteins.

Applicant argues that the animal of Invention II is related to depression as is the unknown agent of Invention V. Clearly an animal is structurally and functionally distinct from an agent of unknown identity and would require an entirely different search. Furthermore, the method of making and using the agent does not require the animal and vice versa.

Applicant has argued that the claims of Invention II and those of Inventions VII-X and XII have not been sufficiently demonstrated to be unrelated. In response, the Examiner has not set forth that the inventions are unrelated. They are patentably distinct methods that are independent of each other. The method included in Invention II is an in vivo method of screening for expression modulators. Inventions VII-X are in vitro methods of screening that do not use the animal or the methods of Invention II. Invention XII is a method of treatment. Invention VII-X and XII have different method steps from the method of Invention II as well as each other. The result of each is different and the goal of each is different.

Applicant argues that the cells, animals, methods of making and using the animals of Invention II are related to the unknown agent that has an effect on depression of Invention XI. Applicant asserts that the two inventions can be searched together. This is not persuasive, especially considering the identity of the agent is unknown. Furthermore, the methods

associated with any of the claims of Invention II are distinct from methods of making or using any agent that has an effect on depression.

Applicant argues the restriction of Inventions III and each of Inventions IV, VI-X and XII are related in some manner to depression and involve the same modes of operation. In response, it is not clear how the various inventions have the same modes of operation. The in vivo methods of identifying an agent that modulates the function of a secreted protein gene of Invention III are not required for the implementation of the in vitro methods of identifying an agent that modulates the expression of a secreted protein gene of Invention IV, the methods of identifying agents that modulate a secreted protein expression using a transgenic mouse comprising a disruption in a secreted protein gene of Invention VI, the methods of identifying an agent that modulates a secreted protein gene function using a cell comprising a secreted protein gene of Invention VII, the in vitro method of identifying an agent that has an effect on depression using a secreted protein of Invention VIII, the in vitro method of identifying an agent that has an effect on depression using a cell expressing a secreted protein gene of Invention IX or X, and a method of treating depression in a patient of Invention XII, and vice versa. Each of the methods requires a separate and materially different protocol. The methods of Invention III and products and methods of Inventions IV-XII are classified differently. The burden required to search Inventions III and any of Inventions IV, VI-X and XII together would be undue.

Applicant argues the restriction of Inventions V and each of III,IV,VI-X or XII are related. In response, the methods of Inventions III, IV, VI-X or XII are not required for the unidentified agent of Invention V and the unidentified agent is not required for the methods.

The methods and the agent are classified differently. The burden required to search any of Inventions III, IV, VI-X or XII and Invention V together would be undue.

Applicant argues the restriction of Inventions XI and each of III,IV,VI-X or XII is improper because the inventions are related and can be examined together without undue burden. In response, Inventions III, IV, VI-X or XII and Invention XI are patentably distinct because the agent of Invention XI can be identified using different methods. The methods of Inventions III, IV, VI-X or XII are not required for the agent and the agent is not required for the methods. The methods and the agent are classified differently. The burden required to search any of Inventions III, IV, VI-X or XII and Invention XI together would be undue.

Applicant argues the restriction of Inventions IV and Inventions VI-X or XII because the inventions are related and have similar method steps. While some of the methods are drawn to in vitro screening methods, the step of monitoring the effect of the agent is different for various inventions and results in identification of different classes of agents (i.e. transcriptional regulators or functional regulators). Other inventions are drawn to in vivo methods. The in vitro methods of identifying an agent that modulates the expression of a secreted protein gene of Invention IV is not required for the methods of identifying agents that modulate a secreted protein expression using a transgenic mouse comprising a disruption in a secreted protein gene of Invention VI, the methods of identifying an agent that modulates a secreted protein gene function using a cell comprising a secreted protein gene of Invention VII, the in vitro method of identifying an agent that has an effect on depression using a secreted protein of Invention VIII, the in vitro method of identifying an agent that has an effect on depression using a cell expressing a secreted protein gene of Invention IX or X, and a method of treating depression in

a patient of Invention XII, and vice versa. Each of the methods requires a separate and materially different protocol. The methods of Invention IV and products and methods of Inventions VI-X and XII are classified differently. The burden required to search Inventions IV and any of Inventions VI-X or XII together would be undue.

Applicant argues the restriction of Inventions V and XI. Applicant argues that the agents have similar function and structure. In response, the Examiner respectfully disagrees. The agents of Invention V as identified as expression modulators whereas that of Invention XI is a functional modulator. These two different classes of agents differ in function and effect and would also differ in structure.

Applicant argues the restriction of Inventions VI and Inventions VII-X or XII because the inventions are related and have similar method steps. While some of the methods are drawn to in vitro screening methods, the step of monitoring the effect of the agent is different for various inventions and results in identification of different classes of agents (i.e. transcriptional regulators or functional regulators). Other inventions are drawn to in vivo methods that would clearly involve in vivo assays as opposed to gene expression or protein expression assays in vitro. The same response applies to Applicant's traversa0l of the restriction requirement relating to Inventions VII and VIII-X or XII as well as VIII-X and XII.

Therefore, the restriction is maintained for the reasons of record set forth on the restriction requirement mailed 06/25/2004.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-4,11-15,22 and 24-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic

or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/27/2004.

Claim Objections

Claim 10 is objected to because of the following informalities: Claim 10 depends from non-elected claim 1. Appropriate correction is required.

Claim 17 is objected to because of the following informalities: Claim 17 depends form itself. For the purposes of examination, claim 17 will be read as though it depends from claim 16. Appropriate correction is required.

Claim 18 is objected to because of the following informalities: Claim 18 depends form itself. For the purposes of examination, claim 18 will be read as though it depends from claim 17. Appropriate correction is required.

Claim 19 is objected to because of the following informalities: Claim 19 requires a pseudopregnant mouse to give birth. A pseudopregnant mouse is not pregnant and cannot give birth. Appropriate correction is required.

Claim 20 is objected to because of the following informalities: Claim 20 depends from itself. It appears that the dependency of claim 20 from claim 20 is a typographical error and the claim is intended to depend from claims 17 or 19. If claim 20 were to depend from claim 19, it would be improper because claim 20 is drawn to a cell derived from a mouse while claim 19 is drawn to a method. Appropriate correction is required.

Claim Rejections - 35 USC § 101/112

Definitions:
[from REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS; repeated from http://www.uspto.gov/web/menu/utility.pdf]

"Credible Utility" - Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong". Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A *credible* utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers. Therefore, the credibility of such an assertion would not be questioned, although such a use might fail the *specific* and *substantial* tests (see below).

"Specific Utility" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material, which has a stated correlation to a predisposition to the onset of a particular disease condition, would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

See also the MPEP § 2107 - 2107.02.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-10, 16-21 and 23 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well-established utility.

The claims are directed to methods of making a transgenic non-human animal whose genome comprises a disruption in a secreted protein gene (claims 10 and 19), the animal (claims 8,16-19), wherein the animal is a mouse exhibiting a behavioral abnormality (claims 16) wherein the behavioral abnormality is an anti-depressive condition (claim 17). Claims 5-7,9 and 20 are drawn to cells comprising a disruption in a secreted protein gene. Claims 21 and 23 are methods of using a mouse comprising a disruption in a secreted protein gene to screen for agents that have an effect on depression.

The instant specification has disclosed that the nucleotide sequence set forth in SEQ ID NO: 1 encodes a secreted protein gene product. The instant specification has further contemplated that disruption of the nucleotide sequence set forth in SEQ ID NO: 1 in a mouse will produce a phenotype of any behavioral abnormality or any anti-depressive condition. The instant specification has purported that such mice may be used to identify agents that modulate or ameliorate a phenotype associated with a disruption in SEQ ID NO: 1.

The specification has provided general teachings that the claimed transgenic non-human animals may be used to identify agents that affect a phenotype related to the mice, including depression.

The instant specification has discussed that the mice of the instant invention can be used as models of disease to screen for drug therapies (page 19, line 16-page 20). However, the evidence of record, while disclosing that the phenotypes exhibited by the claimed transgenic mice are consistent with symptoms associated with a secreted protein gene, does not provide a correlation between the phenotype of the claimed mouse, disruption of a secreted protein gene and any disease or disorder. The specification has taught that the claimed mouse exhibits decreased time spent immobile in the tail suspension test as compared to a wild-type mouse (page 54, lines 16-18). The specification teaches that this is an indication of less of a propensity for endogenous depression but does not define to what this vague phenotype correlates. For example, less time immobile in the tail suspension test could merely indicate a mouse that has a physiological aversion to being immobile as a result of a neurological abnormality (tremor, shakes, involuntary movement) or behavioral abnormality such as hyperactivity. The specification does not link this test result to those of other behavioral tests

and does not demonstrate that the mouse is actually less likely to develop depression. Therefore, the specification does not even allow one of ordinary skill in the art to guess at what an agent identified as capable of affecting the phenotype of the claimed mouse can be used for in the real world. As set forth in the utility guidelines, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed. Similarly, a statement of therapeutic utility for an unspecified disease is non-specific. Therefore the claimed mice lack a specific utility. The usefulness of the mutant mice as models is not clear without assessing that they specifically reflect a disease, leaving the skilled artisan to speculate the uses of the transgenic mouse and other species of transgenic non-human animals encompassed by the claims. Furthermore, under the utility guidelines set forth above, requirement for further research or experimentation renders the claimed invention as lacking a substantial utility. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. The evidence of record has not provided any other utilities for the transgenic mouse encompassed by the claims that are specific and substantial.

Crawley (1999, Brain Research, Vol. 835, pages 18-26) has taught that targeted gene mutation is designed to address specific hypotheses about the behavioral role of a gene. The specific behavioral tasks are designed around the hypothesis. Genes encoding various types of proteins expressed in various patterns will be hypothesized to affect specific behavioral tasks depending upon the characteristics of the gene in question. According to Crawley, a thorough knowledge of the behavioral literature is required to choose the optimal constellation of

behavioral tests to address the critical hypotheses" (page 20, col. 1, paragraph 2). Crawley further teaches that each task has its own limitations and that multiple tasks must be chosen based on knowledge of behavioral neuroscience taking into consideration the characteristics of the gene in question (page 20, col. 2, paragraph 2). In the instant case, the gene knocked out, that encoding a polypeptide that is also encoded by the EST cDNA set forth by SEQ ID NO:1, has not been characterized. Only a short sequence relating to the gene is provided and it appears to have been only hypothesized that the EST encodes a protein that is secreted. The specification has not demonstrated that the protein is secreted or that it has any role in any physiological process that would affect the behavioral performance of the mouse. Therefore, it cannot be concluded, that the claimed mice exhibit an anti-depressive condition related to depression. The mice could merely be overly active or have increased fear of being held upside down. Further characterization of the gene in question and of the mouse are needed to define the phenotype of the claimed animals.

The art has taught that time spent immobile in the tail suspension test using wild-type mice can be used as a criteria in screening anti-depressive drugs for treating depression (refer to Yoshikawa, 2002, Genome Research, Vol. 12, pages 357-366, specifically paragraph bridging columns at page 357; Gass, 2001, Physiology and Behavior, Vol. 73, pages 811-825, specifically paragraph bridging columns at page 815 and page 815, col. 2, paragraph 2). It is known that anti-depressants counter the natural response of a wild-type mouse of remaining immobile when held by the tail. However, it cannot be found in the art of record that decreased immobility in the tail suspension test correlates with a model of decreased propensity towards depression or any other behavioral condition. Furthermore, how one would use a

model animal that is "less depressed" or less likely to become depressed is not set forth by the specification. If an animal is less likely to become depressed, it isn't clear how that animal can be used to screen for agents to treat depression (specifically see claims 21 and 23) or what other disease that animal can be used as a model for.

Therefore, the art clearly suggests a need to provide independent evidence of an association of an antidepressive phenotype associated with depression with the described secreted protein gene and a disease or disorder. However, neither the specification nor any art of record provides evidence of the existence of such a correlation. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the transgenic mouse encompassed by the claims. Therefore, a mouse exhibiting a phenotype of decreased time spent immobile in the tail suspension test is neither credible nor substantial.

The claimed cells lack credible, specific and substantial utility for the reasons above and because the specification does not teach how to use the cells in any manner other than to make the mouse or when they are part of a mouse that is a model of disease. The claimed methods lack patentable utility for the reason above. Without further experimentation, the utility of the mouse in identifying an agent that has an effect on depression is not substantial or credible.

In light of the above, the skilled artisan would not find the asserted utility of the transgenic mouse, targeting construct and cells encompassed by the claims to be credible, specific or substantial.

Enablement

Claims 5-10,16-21 and 23 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 5-10,16-21 and 23 are further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims lack enablement in addition to the reason set forth pertaining to utility as forth below.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or

unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The claims are broadly written in a number of respects including the genera of secreted protein genes, the species of non-human animal and the scope of the phenotype encompassed by the terms behavior abnormality and anti-depressive condition. Specifically, claims 5-7, 9 and 20 are directed to cells, encompassing cells in vivo and in vitro, comprising a disruption in any secreted protein gene. Claim 8 is directed to any non-human species of animal comprising a disruption in any secreted protein gene wherein the animal exhibits any phenotype. Claims 10 and 19 are directed to methods of making a transgenic mouse comprising a disruption in any secreted protein encoding gene. Claim 16 is drawn to a transgenic mouse comprising a disruption in any secreted protein gene wherein the mouse exhibits any behavioral abnormality and claim 17 limits the behavioral abnormality to any anti-depressive condition. Claim 18 limits the anti-depressive condition to one characterized by decreased time spent immobile in a tail suspension test. Claims 21 and 23 are drawn to methods of screening for an agent that has an effect on depression using any behavioral test.

The state of the art at the time of filing was such that one of skill could not predict the phenotype of transgenics, including knockout mice. Leonard (1995, Immunological Reviews, Vol. 148, pages 98-113) disclosed mice with a disruption in the g_c gene that was intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Griffiths (1998, Microscopy Research and

Technique, Vol. 41, pages 344-358) taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph).

The art at the time of filing further held that targeted gene insertion technology was not available for any species other than mouse. Since homologous recombination is required for gene targeting methods, embryonic stem cell technology must be available to carry out the method. Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) teach that non-mouse ES cells capable of providing germline chimeras were not available (page S38, column 1, first paragraph). Campbell and Wilmut (1997, Theriogenology, vol. 47, pp, 63-72) acknowledge reports of ES-like cells in a number of species, but emphasize that as yet there are no reports of any cells lines that contribute to the germ line in any species other than mouse (page 65).

1) The specification does not provide adequate guidance for one of skill in the art to make and use non-human transgenic animals having a disruption in a secreted protein gene in any species other than mouse. The methods of gene targeting such as employed in the instant invention require embryonic stem cells. As stated above, the state of the art at the time of filing was that ES cell technology was not available for targeted mutagenesis in any species other than mouse. The specification discloses introducing cells comprising a disruption a secreted protein gene into a blastocyst to generate transgenic animals (page 15, lines 1-14). However, the specification and the art at the time of filing fail to disclose any ES cells other than mouse ES cells that contribute to the germline. Therefore, the guidance offered in the specification is limited to the production of knockout mice using totipotent mouse ES cells and no teachings or guidance are offered in regard to how one would have prepared any other

species of animal using targeted mutagenesis. Without such guidance, it would require undue experimentation for one of skill in the art at the time of filing to make any transgenic, non-human animal, other than mouse, with a disruption in a secreted protein gene.

2) Applicants fail to enable making and/or using a transgenic secreted protein gene knockout animal having a phenotype other than less time immobile in the tail suspension test. Claims encompass any phenotype at all, including wild-type (claim 8) as well as any behavioral abnormality (claim 16) or any anti-depressive condition (claim 17). As set forth above, the state of the art at the time of filing held that the phenotype of transgenic knockout mice was unpredictable. Therefore, it is not within the realm of routine experimentation to determine how to make the claimed animals such that they exhibit any phenotype other than that described in the instant specification including less time immobile in the tail suspension test. Furthermore, as set forth in the utility rejection above, the skilled artisan would not know how to use the mouse of claim 18 wherein the mouse exhibits less time spent immobile in the tail suspension test. The specification has not provided adequate support to definitively correlate the observed performance of the mouse in the tail suspension test with an anti-depressive condition (see above). The specification has not demonstrated how to make the claimed mice other than that which exhibits less time immobile in the tail suspension test. Without such guidance as to how to make and use a transgenic secreted protein gene knockout mouse having any and all possible phenotypes, it would require one of skill in the art at the time the invention was made, undue experimentation to make and/or use the invention as broadly claimed.

3) The specification fails to enable disrupting any secreted protein gene in a mouse or any other species or a cell other than a mouse cell. The art at the time of filing demonstrates a

large genus of genes encoding secreted proteins. The specification only teaches one secreted protein gene, that which is encoded by the partial cDNA set forth by SEQ ID NO: 1. While it would be routine experimentation to knock out any known secreted protein gene, as set forth above, the phenotype of those mice would not be predictable and therefore, the person of ordinary skill in the art would not know how to use the mice comprising a disruption in any secreted protein gene without further, undue characterization and experimentation with the mice.

4) The specification does not enable making a mouse that is heterozygous for a disruption a secreted protein gene with the phenotypes encompassed by claims 16-18. As set forth in the art, the phenotype of a transgenic, knockout animal was unpredictable at the time of filing. The specification does not teach how to make a mouse heterozygous for a disruption in a secreted-protein gene that displays any phenotype other than wildtype. Thus, the specification does not overcome the unpredictability inherent in generating knockout mice such that any phenotype in heterozygous secreted protein gene knockout mice can be obtained. Without such guidance, it would require one of skill in the art at the time the invention was made, undue experimentation to determine how to obtain make a mouse that is heterozygous for a disruption the secreted protein gene with the phenotypes of claims 16-18 including a behavioral abnormality, an anti-depressive condition or decreased time spent immobile in the tail suspension test.

5) The breadth of claims 8,10,16-19, 21 and 23 is such that they encompass chimeric mice (genetic mosaics) or other animal species (claim 8) wherein only a portion of the cells of the mouse comprises the claimed genetic disruption. Similarly, the claims encompass

disruption of a secreted protein that is extrachromosomal. The specification fails to enable making and using chimeric mice such that they exhibit any phenotype, including a behavioral abnormality or an anti-depressive condition. Inherent in the art of making genetic mosaic animals is the unpredictability of how many and which cells will comprise a genetic alteration. The specification does not provide guidance on the production of a chimeric mouse comprising a disruption in a secreted protein gene, where only some portion of the mouse's cells have the disruption and the mouse also has the claimed phenotypes. At the time of filing it would have been required of the skilled artisan to perform an undue amount of experimentation without a predictable degree of success how to make and use the chimeric mice encompassed by the claims. Applicant should overcome this aspect of the rejection by adopting claim language such as "a transgenic mouse whose genome comprises a disruption in a secreted protein gene." Such claim language would also address the aspect of the rejection with respect to the breadth encompassing extrachromosomal gene disruptions.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction and/or guidance provided by the specification, the underdeveloped art with respect to totipotency of embryonic stem cells in non-mouse species, the unpredictability of phenotype of transgenic animals, and the breadth of the claims with respect to the broad genus of secreted protein genes, it would have required undue experimentation for one skilled in the art to make and use the claimed invention with a reasonable expectation of success.

Written Description

Claims 5-10,16-21 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The claimed invention as a whole is not adequately described if the claims require essential or critical elements that are not adequately described in the specification and that is not conventional in the art as of applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641,1646 (1998).

The claims are written such that they encompass a disruption in any secreted protein gene. The specification fails to describe knocking out any secreted protein gene other than the gene encoding the same secreted protein as the cDNA set forth by SEQ ID NO:1. The specification is clearly drawn to a specific knockout mouse wherein the gene encoding the

same secreted protein as the cDNA set forth by SEQ ID NO:1 is disrupted. The art clearly sets forth that there are a very large number of gene products that are secreted and that these products have diverse physiological roles such as nutrient transport, immune response, cell signaling, cell growth, differentiation and neural signal transduction to name a few. The diversity of secreted proteins known in the art is highlighted by Alberts in Molecular Biology of the Cell (Garland Publishing, Inc. New York and London, 3rd Edition) at pages 722-723. The specification provides no support relating to the structure or the function of any other secreted protein gene other than that which encodes the secreted protein that is encoded by the cDNA set forth in SEQ ID NO:1. There is no indication in the specification at all that Applicant's invention involves any secreted protein gene other than wherein the gene encodes the same secreted protein as the cDNA set forth by SEQ ID NO:1. Therefore, the claims clearly encompass a genus of secreted protein genes that are not described by the instant specification.

In analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the claimed invention encompasses a knockout of a secreted protein gene wherein the secreted protein gene is any gene encoding a protein that is secreted from a cell. In the instant case, the claimed embodiments of any secreted protein encompassed within the genera lack a written description. The specification fails to describe what secreted proteins fall into this genus and it was unknown as of Applicant's effective filing date that the various species of animals encompassed by the claims would have the property of the transgenic mouse described wherein the genome of the mouse comprises a disruption in the gene encoding the

secreted protein that is encoded by the cDNA set froth by SEQ ID NO:1. The skilled artisan cannot envision the detailed chemical structure of the encompassed animal species or cells, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the large genera recited in the claims at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1) Claims 5-10,19 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Bucay (1998, Genes and Development, Vol. 12, pages 1260-1268).

Claims are drawn to a cell comprising a disruption in a secreted protein gene (claim 5), wherein the cell is a murine cell (claim 6) or and embryonic stem cell (claim 7). Claims are also drawn to a non-human transgenic animal comprising a disruption in a secreted protein gene (claim 8) and a cell derived from said animal (claim 9). Claims 10 and 19 are drawn to methods of making a transgenic mouse comprising a disruption in a secreted protein encoding gene. Claim 19 contains a phenotypic limitation in the preamble that is given little patentable weight as it does not affect the method steps of the claim or the product produced. Claim 20 depends from claim 17 and from itself. However, if the improper dependency is an error and the claim were to depend from claim 19, it would encompass a cell from the mouse made by the method of claim 19.

Bucay taught generating a transgenic mouse comprising a disruption in the osteoprotegerin gene, which is a secreted protein. Bucay taught making a mouse ES cell comprising a disruption in the osteoprotegerin gene, satisfying the limitations of claims 5-7. Bucay used this ES cell to generate a transgenic mouse comprising a disruption in the osteoprotegerin gene by introducing the ES cell into a blastocyst and generating a chimeric mouse and mating the chimeric mice to generate a transgenic mouse, which satisfies the limitations of claims 8,10 and 19. See page 1266, col. 2, paragraph 1. Bucay also taught cells derived from the mice as the mice are comprised of cells and Bucay observed the histology of the cells (for example see Figures 4 and 5).

Therefore, Bucay taught all of the limitations of claims 5-10,19 and 20.

2) Claims 5-10,19 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang (1997, Science, Vol. 276, pages 1408-1412).

Claims are drawn to a cell comprising a disruption in a secreted protein gene (claim 5), wherein the cell is a murine cell (claim 6) or and embryonic stem cell (claim 7). Claims are also drawn to a non-human transgenic animal comprising a disruption in a secreted protein gene (claim 8) and a cell derived from said animal (claim 9). Claims 10 and 19 are drawn to methods of making a transgenic mouse comprising a disruption in a secreted protein encoding gene. Claim 19 contains a phenotypic limitation in the preamble that is given little patentable weight as it does not affect the method steps of the claim or the product produced. Claim 20 depends from claim 17 and from itself. However, if the improper dependency is an error and the claim were to depend from claim 19, it would encompass a cell from the mouse made by the method of claim 19.

Zhang taught generating a transgenic mouse comprising a disruption in the UG gene, which is a secreted protein. Zhang taught making a mouse ES cell comprising a disruption in the UG gene, satisfying the limitations of claims 5-7. Zhang used this ES cell to generate a transgenic mouse comprising a disruption in the UG gene by introducing the ES cell into a mouse blastocyst and generating a chimeric mouse and mating the chimeric mice to generate a transgenic mouse, which satisfies the limitations of claims 8,10 and 19. See page 1408, col.2, paragraph 2. Zhang also taught cells derived from the mice as the mice are comprised of cells and Zhang observed the histology of the cells (for example see Figure 2).

Therefore, Zhang taught all of the limitations of claims 5-10,19 and 20.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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